

# Epidemiology of inherited cerebellar ataxias and challenges in clinical research

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## Abstract

Cerebellar ataxia is a clinically heterogeneous group of disorders, which includes several well-characterized genetic diseases as well as sporadic ataxias. The pathophysiology of ataxia is being understood, and a mechanistic basis for the appearance of these disorders is progressively emerging. Novel genes associated with dominant and recessive ataxias are being steadily identified, and research on their pathomechanisms not only has led to understanding the etiology and underlying cause for the development of ataxia but also has steered the field towards future therapeutic regime, aiming to control and prevent some forms of these diseases. Nevertheless, lack of knowledge for the causation of disease in a sizeable proportion of patient remains, and this issue is further compounded by the rarity of some of these ataxias as well as their restricted geographical distribution. On the other hand, large collaborative studies are providing critical information on the clinical spectrum, progression, and pathophysiology of inherited and sporadic ataxias. In the following sections, we describe the epidemiology, symptoms, pathological progression, and clinical management of various forms of inherited cerebellar ataxias. Finally, we provide a perspective on the challenges faced by the field in translational research and the development of successful therapeutic modalities for patients.

## Keywords

Ataxia, spinocerebellar ataxia, episodic ataxia, genetics of cerebellar diseases, mechanisms of Purkinje cell degeneration, therapies

## Introduction

*Ataxia* refers to movements that are poorly coordinated, originally derived from Greek, meaning lack of order. Dysfunction of the cerebellum and its input or output tracts can lead to the development of ataxia.<sup>1,2</sup> In some cases, there is a combined involvement of cerebellar and extracerebellar structures, particularly the brainstem. Loss of proprioceptive sensory feedback during movement and stance due to the loss of function of muscle spindles leads to the development of afferent ataxia, and symptoms are located to the peripheral nerves localized to the, dorsal root ganglia (DRG), and spinal cord.<sup>3</sup> Current, global epidemiological studies on ataxia have estimated an overall ataxia occurrence rate of 26/100,000 in children, and for dominant hereditary cerebellar ataxia an occurrence rate of 2.7/100,000, and the frequency of recessive hereditary cerebellar ataxia as 3.3/100,000.<sup>4–7</sup> The general rarity of ataxias as a whole and the involvement of multitude of genetic factors

coupled with variable disease progression rates and diagnosis makes the field of ataxias highly challenging and distinct from other neurodegenerative diseases.

## Hereditary ataxias

Hereditary ataxia is a large and multifaceted group of diseases affecting the cerebellum and its connections, all

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characterized by the development of ataxia as an early and dominant feature of the disease. Nevertheless, the genetic, pathophysiological, clinical, and neuropathological features of these diseases are quite heterogeneous and varied. Majority of the hereditary ataxias are transmitted as autosomal dominant or autosomal recessive traits, episodic ataxias (EAs) have an autosomal dominant inheritance pattern, and eight subtypes have been defined based on genetic mutations and clinical characteristics. X-linked ataxias are rare, with fragile X tremor ataxia syndrome (fragile X-associated tremor/ataxia syndrome) being the most common in this group of ataxias. Mitochondrial DNA (mtDNA) mutations may lead to the development of ataxia together with the presence of other debilitating neurological symptoms. Point mutations in mtDNA are maternally transferred; single deletions of mtDNA are often sporadic in nature, while multiple mtDNA deletions and mtDNA depletion occur due to inherited dominant or recessive nuclear DNA mutations. Congenital ataxias are developmental disorders of the cerebellum, inherited in an autosomal or X-linked recessive manner.

### *Autosomal dominant cerebellar ataxia*

Spinocerebellar ataxia (SCA) is a complex group of dominantly inherited degenerative ataxias, numbered chronologically following their discovery order. Some exceptions to the rule include SCA24, an autosomal recessive ataxia; SCA29, a congenital nonprogressive ataxia; and SCA15/16 and 19/22 which are allelic disorders. More than 49 SCA forms attributed to at least 37 genes have been identified, showing ethnic differences in their frequency and distribution,<sup>1</sup> with an incidence of 3 per 100,000 in the European population.<sup>8</sup> The major clinical feature is impairment in motor coordination and loss of movements, arising not only due to the progressive loss of Purkinje cells in the cerebellum but also due to degenerative changes in the brain stem and spinocerebellar tracts, causing neurological symptoms involving pyramidal and extrapyramidal manifestations.

The principal cause of the most common SCAs (SCA1, 2, 3, 6, 7, and 17) is a CAG trinucleotide repeat expansion in specific genes, causing an expanded polyglutamine tract (PolyQ) in the encoded proteins.<sup>9</sup> These long PolyQ repeats cause misfolding of proteins, which aggregate, forming inclusions in the cytoplasm or nucleus of vulnerable neurons, invariably contributing to the progression of the pathology, neuronal dysfunctions, and subsequent neuronal degeneration. The clinical prognosis depends on the length of repeat expansion, and an inverse correlation exists between the age of symptoms onset and the repeat length, a phenomenon termed as anticipation. The anticipation involves an increase in the length of expansion in subsequent generations, leading to an early development of symptoms than the previous generation.<sup>10</sup> The clinical symptoms of PolyQ SCAs usually appear during adulthood, between the third and the fifth decades of life,<sup>11</sup> with

consequent worsening and severe progression of the symptoms, culminating in death due to brainstem failure. The first telltale symptom for a wide range of SCAs is the appearance of abnormal gait, with additional manifestations depending on the mutated gene such as impaired handwriting, dysarthria, intellectual disability, impaired control of eye movement, and pyramidal and extrapyramidal signs. An enigmatic question that remains to be deciphered is why certain neurons are exclusively affected, since majority of the SCA-associated proteins are widely expressed in different cell types, but predominantly Purkinje cells are susceptible to neurodegeneration. In the following paragraphs, we describe the most common SCAs and their characteristics in detail.

### **SCA1**

SCA1 is caused by CAG expansion of more than 40 repeats in the *ATXN1* gene, encoding for Ataxin-1 protein, resulting in a toxic gain of function of Ataxin-1 protein leading to tissue-specific neuronal loss. In humans and rodent model of SCA1, Ataxin-1 is widely expressed throughout the body, but Purkinje cells remain most vulnerable to the mutated protein. The typical pathology observed in SCA1 patients involves primarily the olivopontocerebellar atrophy, loss of Purkinje cells, degeneration of different brainstem areas like basal pontine, and olivary nuclei and the association of some of the cranial nerve nuclei involved in motor control.<sup>8,12</sup> In the spinal cord, degeneration of the anterior horns, Clarke's column, posterior columns, and spinocerebellar tracts are observed.<sup>13,14</sup> In some SCA1 cases, minor neuronal loss is present in the basal forebrain cholinergic nuclei, cerebral cortex, and hippocampus.<sup>13,14</sup>

Ataxin-1 normally shuttles between the cytoplasm and the nucleus of the cells, and the PolyQ expansion interferes with this intra-organellar shuttling, leading to the retention of the protein within the nucleus. Moreover, the presence of specific domains within the Ataxin-1 protein such as AXH domain has been implicated in RNA binding and self-association and through this domain Ataxin-1 is able to bind different proteins involved in RNA metabolism, binding, and transcription regulation.<sup>15–18</sup> In murine models of SCA1, impairment in protein interactions and dysfunctions in RNA processing are key processes involved in SCA1-associated degeneration.<sup>19</sup> Majority of wild-type and expanded Ataxin-1 assembles into large stable complexes together with transcriptional repressor Capicua (CIC), directly modulating CIC repressor activity in mammalian cells, and a gain of function of this mechanism drives cerebellar toxicity in SCA1.<sup>20,21</sup> Early disease-related alterations in critical intracellular pathways crucial for neuronal functioning, that is, glutamate receptor signaling and mechanistic target of rapamycin signaling, serving as important integrators of biological metabolism and cellular homeostasis have been implicated in the pathology of SCA1.<sup>22,23</sup> Mitochondrial dysfunctions and impairments

in electron chain transport complexes have been observed in preclinical models of SCA1, and ameliorating mitochondrial functioning deaccelerated the progression of the pathology.<sup>24,25</sup> Moreover, functional and morphological alterations in the cerebellar circuitry involving both excitatory and inhibitory inputs onto Purkinje cells,<sup>26–29</sup> as well as changes in intrinsic pacemaker firing of Purkinje cells,<sup>30</sup> are observed, coinciding with specific disease stage.

## SCA2

PolyQ expansion in the *ATXN2* gene causes SCA2 pathology. The age of onset for SCA2 can vary from infancy to late adult life; infantile forms of SCA2 are mainly due to hyper-expanded CAG repeats. SCA2 patients manifest ataxia, slow saccadic eye movements, hyporeflexia, sensory neuropathy, ocular palsies, and some degree of cognitive impairment. Parkinsonism form of tremor is observed due to the degeneration of dopaminergic neurons in the substantia nigra.<sup>31</sup> Similar to SCA1, most SCA2 patients display olivopontocerebellar atrophy and comparable cerebellar cortical modifications; however, unlike SCA1 the deep cerebellar nuclei remain largely spared in SCA2.<sup>32–34</sup> Atrophy of the spinal anterior horn and degeneration of spinocerebellar tracts and posterior columns are present.<sup>32,33</sup> SCA2 CAG repeats whose length is at the limit between normal and expanded alleles, though overall very rare, are found significantly more often in patients with amyotrophic lateral sclerosis (ALS),<sup>35</sup> a risk factor for sporadic ALS<sup>36</sup> and modifiers in chromosome 9 open reading frame 72 (*C9ORF72*) carriers, rendering susceptibility to ALS rather than frontotemporal lobar degeneration. *ATXN2* CAG repeat, interrupted by trinucleotide CAA, is observed in patients exhibiting prominent parkinsonism-associated features and levodopa responsiveness.<sup>37–39</sup>

Several important studies have implicated Ataxin-2 protein in playing a crucial role in RNA metabolism, strengthened by evidences showing that Ataxin-2 interacting proteins such as polyA-binding protein (PABP) and RNA-binding protein called Ataxin-2 binding protein interacted with Ataxin-2 via the PABP-interacting motif, PAM2.<sup>40,41</sup> Ataxin-2 is also involved in the assembly of stress granules and P-bodies, major vesicular sites for the regulation of both mRNA translation and degradation.<sup>42</sup> As intermediate CAG tract-repeat lengths in Ataxin-2 are a risk factor for ALS, primarily in TDP-43 (43 kDa TAR DNA-binding protein)-related ALS, similar to Ataxin-2, TDP43 functions in regulating RNA metabolism, indicating that both the proteins might be involved in controlling a common RNA metabolism pathway.<sup>43</sup>

## SCA3

SCA3, also termed as Machado–Joseph disease, is caused by an unstable CAG trinucleotide repeat in the *ATXN3* gene. In comparison to SCA1 and SCA2, cerebellar cortex

and olivary nuclei are not majorly affected, and severe degenerative pathology is present in the pontine nuclei and deep cerebellar nuclei.<sup>44,45</sup> Moreover, substantia nigra, globus pallidus, and subthalamic nuclei are also affected to a certain extent but not observed in all patients.<sup>46</sup> The clinical symptoms are highly variable from very early onset reported in young people to late onset, manifesting as dysarthria, oculomotor dysfunctions, rigidity, pyramidal signs, and neuropsychological defects. This variable disease onset and progression is classified into four different SCA3 subtypes: type 1 is referred to as early onset and patients exhibit stiffness and spasticity with nominal ataxia; type 2 appears in midlife with the development of progressively increasing ataxia; type 3 has a late-in-life onset and symptoms also involve a neuropathic component; and type 4 occurs in patients who manifest the disease with a strong parkinsonism component.<sup>13,47</sup>

Ataxin-3 is a relatively small protein (42 kD) shuttling between the cytoplasm and the nucleus of the cells. Wild-type Ataxin-3 appears particularly abundant in the cytoplasm; however in the affected neurons it tends to accumulate in the nucleus<sup>48</sup> and is primarily involved in quality control of proteins, working as a dedicated deubiquitinase (DUB). Currently, the precise pathogenesis of the disease remains unclear, as in vivo study demonstrated that mice lacking Ataxin-3 are normal except for the progressive accumulation of polyubiquitin-positive proteins in the brain. One plausible explanation for the pathogenesis of SCA3 is that the conformational changes occurring in the Ataxin-3 could alter the DUB function in multiple pathways involved in the ubiquitin protein control.<sup>8</sup> Intriguingly and contrarily to expectations, the elimination of Ataxin-3 from one of the transgenic mice line of yet another common PolyQ expansion disease, that is, Huntington's disease (HD), did not accelerate the major symptoms of the HD pathology.<sup>49</sup>

## SCA6

The affected gene in SCA6 encodes for  $\alpha 1A$  transmembrane subunit of the P/Q-type voltage-gated calcium channel Cav2.1.<sup>50,51</sup> In contrast to other SCAs, SCA6 is considered a pure cerebellar disease because other brain parts that are primarily affected in other SCAs seem to be variably and negligibly affected in SCA6 patients.<sup>52</sup> Calcium homeostasis is a fundamental biological process in neurons, tightly regulated via the expression of several calcium channels. Interestingly, the Cav2.1 calcium channel is particularly abundant in the primarily affected neurons in SCAs of the Purkinje cells. To date, the possibility that the mutation per se affects the functionality of the Cav2.1 channel, leading to the development of SCA6, is highly debated. An alternative mechanism for toxicity involves the generation of an expanded polyQ-containing C-terminal domain via a process of cleavage of either  $\alpha 1A$  subunit<sup>53</sup> or generation of  $\alpha 1ACT$  a transcription factor

through the translation of an internal ribosomal entry site in *Cav2.1* gene contributing to the pathology due to their nuclear retention.<sup>54</sup>

### Other PolyQ-linked SCAs

Three other PolyQ diseases, such as SCA7, SCA17, and dentatorubral-pallidoluysian atrophy (DRPLA), are caused due to CAG expansions in defined genes.<sup>55,56,57,58</sup> In the case of SCA7, the expansion is observed in the *ATXN7* gene, and the pathophysiological and clinical etiology is similar to those observed in SCA1, 2, and 3. Unique to SCA7 is the presence of widespread retinal degeneration.<sup>59</sup> SCA17 is very rare, caused by a repeat expansion in the TATA box-binding protein (TBP) encoded by the *TDP* gene, which is involved in general transcription.<sup>56</sup> The PolyQ expansion might interfere with TBP-mediated neuronal cell-specific transcription, thereby causing neurodegeneration. DRPLA is also very rare, and patients present strikingly heterogeneous clinical symptoms.

### Autosomal dominant spinocerebellar ataxia due to non-coding repeat expansions

In a subset of SCAs such as SCA10, 12, 31, and 36, the expansions occur within the non-coding region of the gene. Non-coding ATTCT microsatellite repeat expansion in the *ATXN10* gene is causally linked to SCA10.<sup>60</sup> This ATTCT repeat is polymorphic, normally having a length of 9 to 32 ATTCT repeats in the overall population, but can expand up to 4500 repeats in SCA10 patients.<sup>60,61</sup> In few cases of SCA10, the 5'-end of the repeat expansion comprises a complex sequence of penta- and hepta-nucleotide interruption motifs that are preceded by a tract of tandem ATCCT repeats of unknown length at its 3'-end.<sup>62</sup> Interestingly, expansions carrying these specific penta- and hepta-nucleotide interruption motifs show the presence of an epileptic seizure phenotype. In SCA31, disease-causing microsatellites comprising of pentanucleotide repeat complexes, including (TGGAA)<sub>n</sub>, (TAGAA)<sub>n</sub>, (TAAATA GAA)<sub>n</sub>, and (TAAAA)<sub>n</sub>, within an intron shared by two different genes, such as brain expressed associated with NEDD41 (*BEAN1*) and thymidine kinase 2 (*TK2*), are involved.<sup>63</sup> RNA foci containing UGGAA repeats in Purkinje cell nuclei of SCA31 patients, but absent in control individuals, implicate (TGGAA)<sub>n</sub> as the crucial motif for SCA31 pathogenesis, most likely via a gain-of-toxic-function mechanism.<sup>64</sup> Recent study has revealed a mechanistic link between RNA and RNA chaperone-TDP-43 in ribonucleoprotein complex homeostasis and SCA31 pathology.<sup>65</sup> In SCA36, a type of SCA accompanied by motor neuron deficits, an intronic GGCCTG hexanucleotide repeat expansion in the *NOP56* gene, is implicated.<sup>66</sup> Due to the presence of GGCCTG repeat, the RNA transcribed from this gene causes nuclear aggregates,

wherein critical RNA binding proteins are trapped, forming RNA foci, leading to the altered expression of crucial genes.<sup>67</sup> A similar repeat expansion mechanism for other neurodegenerative diseases such as in *C9ORF72*-associated ALS is postulated.<sup>68</sup>

### Other forms of autosomal dominant spinocerebellar ataxia

The remaining SCAs do not show repeat expansion but occur due to point mutations or deletions in the specific genes. In most of the cases, the mutation is present within genes, which encode for proteins important for normal functioning of the cerebellum (see Table 1 for the description of genetic mutations and the symptoms of various autosomal dominant spinocerebellar ataxias). An interesting example is that of mutations in the gene encoding for  $\beta$ -III spectrin (*SPTBN2*), which lead to the development of two human neurodegenerative diseases involving gait ataxia and cerebellar atrophy. One of them is SCA type-5 (SCA5)<sup>69</sup>, and the other is spectrin-associated autosomal recessive cerebellar ataxia type-1.<sup>70</sup> In majority of SCAs belonging to this group, implicated mutations are in genes coding for proteins functioning in calcium homeostasis, ion channels, mitochondria, cytoskeleton, and other intracellular pathways to which cerebellar Purkinje cells are especially dependent on for their proper functioning. Heterozygous loss-of-function mutations clustering within the proteolytic domain of AFG3L2, a mitochondrial resident protein, cause SCA28 (Di Bella et al., 2010). AFG3L2 belongs to the AAA protease superfamily, assembling together with paraplegin in the inner mitochondrial membrane into homo-oligomers and hetero-oligomers, exerting chaperone-like activity on respiratory chain complexes, regulating the processing of the mitochondrial profusion protein OPA1 and the subunit of mitochondrial ribosomes MRPL32.<sup>71–73</sup> Similarly, in SCA19/22 patients, mutations in the voltage-gated potassium channel Kv4.3-encoding gene *KCND3* highlight the important role of ion channels as not only main regulators of neuronal excitability but also in the pathogenesis of cerebellar Purkinje cell degeneration.<sup>74</sup>

### Autosomal recessive cerebellar ataxias

Autosomal recessive cerebellar ataxias (ARCAs) are characterized by abnormal development and neurodegeneration of the cerebellum and the spinal cord. Most ARCAs have symptom onset during childhood or adolescent years, but similar to SCAs variability is considerable and is inversely dependent on the expansion size. As in the case of SCAs, the first symptom to appear is gait imbalance, followed by limb ataxia and dysarthria. The most frequent autosomal recessive ataxia is Friedreich ataxia (FRDA), with a population frequency of 1–2:50,000, caused by the mutation in the *FXN* gene that encodes for the Frataxin protein leading to loss of its function.<sup>75</sup> In European populations, the

**Table 1.** Mutations and symptoms linked to autosomal dominant spinocerebellar ataxias.<sup>a</sup>

SCA	Gene	Type of mutation	Symptoms
SCA1	ATXN1	(CAG) <i>n</i>	Pyramidal features, active reflexes, peripheral neuropathy, and ophthalmoparesis
SCA2	ATXN2	(CAG) <i>n</i>	Motor neuron involvement, peripheral neuropathy, slow saccades, parkinsonian features, myoclonus, and dementia
SCA3	ATXN3	(CAG) <i>n</i>	Pyramidal features, motor neuron involvement, peripheral neuropathy, eyelid retraction, and parkinsonian features
SCA4	16q21.1	Unknown	Peripheral neuropathy and pyramidal signs
SCA5	SPTBN2	Point mutations	Tremor and facial myokymia
SCA6	CACNA1A	(CAG) <i>n</i>	Dysphagia, tremor, and somatosensory deficits
SCA7	ATXN7	(CAG) <i>n</i>	Slow saccades, retinal macular degeneration, and dementia
SCA8	ATXN8	(CTG* <i>CAG</i> ) <i>n</i>	Pyramidal signs
SCA10	ATXN10	(ATTCT) <i>n</i>	Dysphagia, seizures, and cognitive impairments
SCA11	TTBK2	Point mutations	Pyramidal signs
SCA12	PPP2R2B	(CAG) <i>n</i>	Peripheral neuropathy, tremor, and parkinsonian features
SCA13	KCNC3	Point mutations	Pyramidal signs and intellectual disability
SCA14	PRKCG	Point mutations	Dystonia and myoclonus
SCA15, 16 and 29	ITPR1	Point mutations, large deletions	Tremor and dystonia
SCA17	TBP	(CAG) <i>n</i>	Parkinsonian features and dementia
SCA18	IFRD1	Point mutations	Peripheral neuropathy
SCA19/22	KCND3	Point mutations, small deletions	Myoclonus and dysphagia (SCA22)
SCA20	Unknown	Genomic duplication	Dysphonia and palatal tremor
SCA21	Unknown	Unknown	Parkinsonian features and mild cognitive impairment
SCA23	PDYN	Point mutations	Pyramidal features
SCA25	Unknown	Unknown	Peripheral neuropathy
SCA26	EEF2	Point mutations	Dysarthria and eye movement abnormalities
SCA27	FGF14	Point mutations	Tremor and dystonia
SCA28	AFG3L2	Point mutations	Pyramidal features and ophthalmoparesis
SCA31	BEAN1	(TGGAA) <i>n</i>	Dystonia
SCA35	TGM6	Point mutations	Tremor and ocular dysmetria
SCA36	NOP56	(GGCCTG) <i>n</i>	Motor neuron involvement
DRPLA	ATN-1	(CAG) <i>n</i>	Myoclonus, epilepsy, and dementia
SCA37	DABI	ATTTC( <i>n</i> )	Gait instability, dysarthria, and eye movement abnormalities
SCA38	ELOVL5	Point mutations	Nystagmus and dysarthria
SCA40	CCDC88C	Point mutations	Ocular dysmetria and tremor
SCA41	TRPC3	Point mutations	Imbalance and gait instability
SCA42	CACNA1G	Point mutations	Gait instability, dysarthria, and nystagmus
SCA43	MME	Point mutations	Peripheral neuropathy, dysarthria, and tremor
SCA44	GRM1	Point mutations	Dysarthria, dysphagia, and dysmetria
SCA45	FAT2	Point mutations	Dysarthria and nystagmus
SCA46	PLD3	Point mutations	Eye movement abnormalities

SCA: spinocerebellar ataxia.

<sup>a</sup>Violet: SCAs with classical PolyQ expansions in the coding region of the gene; blue: SCAs with repeat expansions in the non-coding region of the gene; black: SCAs arising due to point mutations or deletions; green: SCAs arising due to as of yet unidentified mutations

occurrence of FRDA varies between 1:20,000 and 1:725,000 and accounts for >1/3 of ARCA in Caucasians, while all other ARCA have a prevalence of one order of magnitude less than FRDA, whereas in Japan, the most common recessive ataxia is ataxia with oculomotor apraxia type 1 (AOA1). Epidemiological studies have found the existence of a west to east frequency gradient in Europe with highest levels in the south of France, north of Spain and Ireland and lowest levels in Scandinavia and Russia.<sup>76</sup> The onset of symptoms usually appears before the age of 25 years, and patients affected by FRDA manifest dysarthria, hyporeflexia, Babinski responses, sensory loss, and cardiomyopathy,<sup>77</sup> with cardiac failure being the common cause

of mortality in FRDA. Major neurological symptoms appear primarily due to the degeneration of DRG neurons, large sensory neurons, and posterior columns. Wide spread degeneration of spinocerebellar and corticospinal tracts of the spinal cord is frequently observed and the dentate nucleus of the cerebellum is affected, thereby causing a cerebellar pathology.<sup>78,79</sup>

Frequently, the mutation consists in the expansion of a GAA-triplet repeat in the first intron of the *FXN* gene, and unlike dominant ataxia, this expansion is not associated with the anticipation phenomena. Majority of FRDA individuals are homozygous for this mutation but in a few cases, the patients carry a compound heterozygous GAA

expansion together with a different mutation (nonsense, missense, deletions, and insertions).<sup>80–82</sup> GAA expansion causes transcriptional silencing of *FXN*, resulting in the expression of a functionally normal Frataxin albeit at very low levels, which are presumed to be estimated at approximately 5–30% of normal levels (reviewed in<sup>83,84</sup>). The encoded protein of *FXN* gene is located in the internal membrane of the mitochondria; biological and physiological roles of the Frataxin protein are not completely elucidated, but, in recent years, studies have provided evidence for a role of Frataxin in iron metabolism.<sup>85</sup> In general, Frataxin is a multifunctional protein involved in different mitochondrial as well as other metabolic pathways. Recent studies indicate that one prominent function of Frataxin is in iron–sulfur cluster biogenesis, where it functions as an allosteric activator of the cysteine desulfurase Nfs1.<sup>86,87</sup> These small inorganic cofactors are involved in many crucial cellular pathways extending from mitochondrial respiration and metabolic processes to DNA synthesis and repair.<sup>88</sup> Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is considered as the second most common recessive ataxia with onset at childhood, presenting cerebellar ataxia, pyramidal spasticity, and peripheral neuropathy.<sup>89</sup> Originally identified in Quebec, cases are currently documented worldwide. ARSACS results due to loss of function mutation in SACS gene encoding for saccin, a 4579-amino acid protein, localizing to the mitochondria and participating in mitochondrial fission. Fibroblasts from ARSACS patients show a hyper-fused mitochondrial network, due to defects in mitochondrial fission as well as Purkinje cell loss which have been documented from patient brain.<sup>90,91</sup> Besides, mitochondrial dysfunction common pathogenic mechanism in recessive ataxias involves DNA repair defects (ataxia telangiectasia (A-T), AOA1, and AOA2), impaired proteostasis and protein quality control (Marinesco-Sjogren syndrome), and vitamin E deficiency (ataxia with vitamin E deficiency). Oxidative stress might be involved and could play an essential role mainly due to the connection with mitochondrial dysfunction as well as DNA damage.<sup>92</sup> Intriguingly, a fraction of recessive ataxias presents metabolic alterations as symptoms such as in Tay–Sachs disease, Sandhoff disease, Niemann-Pick disease type C, leukodystrophies, cerebrotendinous xanthomatosis, and carbohydrate–glycoprotein deficiency type 1a, seeming to be milder variants of metabolic diseases, eventually making diagnosis difficult.<sup>93</sup> In yet another common recessive cerebellar ataxia, A-T, there is an early and progressive onset of ataxia, oculomotor apraxia, and immunodeficiency, and majority of cases ataxia symptoms appear around 4 years of age.<sup>75</sup> Telangiectasia is the second symptom to manifest, appearing immediately after the development of cerebellar ataxia. The early onset of the symptoms causes severe disability and forces the patients to be wheelchair bound within few years after symptoms onset. The mutation in the *ATM* gene results in a mutated protein belonging to the

phosphoinositol-3 kinase-like serine/threonine kinases family, playing a key role in critical checkpoint of the cell cycle and of the DNA repair. A large number of patients concomitantly develop leukemia and lymphoma with high malignancy.<sup>94,95</sup>

### *Congenital ataxias*

This group of ataxias mainly includes cerebellar structural malformations, which compromises motor development, and patients exhibit a form of stable nonprogressive ataxia. Besides cerebellar and motor deficits, structural malformations affect also other regions of the CNS, and patients exhibit hypotonia, apraxia, episodes of apnea, and cognitive disabilities. Joubert syndrome and associated disorders are the most common genetic congenital ataxias and belong to a group of disorders termed as ciliopathies, which mainly arises due to mutations in genes encoding for proteins of the primary cilium, a microtubule containing extension of the cell membrane essential for the development of many tissues.<sup>96,97</sup> Hence, it is not surprising that Joubert's patients often exhibit structural and functional malformations of other organs such as eyes, kidney, and liver.

### *X-linked degenerative ataxias*

The major X-linked ataxia is FXTAS, a condition occurring in carriers of intermediate length (premutation) alleles (50–200 triplets) of the CGG repeat whose full expansion (9200 triplets) causes the fragile X syndrome of mental retardation. Higher prevalence of FXTAS is present in men around 50 years of age, characterized by the appearance of ataxia and tremor. Notably, FXTAS also occurs in women, but here the clinical manifestation of fragile X permutation is premature ovarian failure rather than the development of ataxia and tremor, indicating that the clinical scenario is highly heterogeneous and complex.<sup>98</sup>

### *Episodic ataxias*

EA belongs to a clinically diverse group of disorders, categorized by regular spells of undefined duration of trunk ataxia and incoordination, which resolves after a certain period.<sup>99,100</sup> The prevalence of EA is less than 1/100,000 but might be underrated due to unidentified causative genes. Most EAs have an autosomal dominant inheritance pattern, although reports of the existence of few sporadic cases are available.<sup>101</sup> The underlying mutations are in genes encoding for ion channels, and based on their clinical features and genetic characterizations, eight subtypes are recognized. The causative gene has been identified for four of them: EA types 1, 2, 5, and 6.

**EA type 1 (EA1)** is associated with mutations in the potassium channel gene *KCNA1* and onset is during early childhood. Patients exhibit brief episodes of ataxia with constant interictal myokymia.<sup>99,100,102</sup> The core features

**Table 2.** Mutations and symptoms associated with episodic ataxias (EAs).

Episodic ataxia	Gene	Protein	Symptoms
EA1	KCNA1	Potassium voltage-gated channel $\alpha 1$ subunit (Kv1.1)	Vertigo, myokymia, epilepsy, dysarthria, weakness, tremor, and incoordination
EA2	CACNA1A	Calcium voltage-gated channel $\alpha 1$ subunit (Cav2.1)	Nystagmus, vertigo, seizure, weakness, dysarthria, dystonia, and cognitive impairment
EA3	Unknown	Unknown	Weakness, vertigo, visual blurring, and headache
EA4	Unknown	Unknown	Vertigo, diplopia, and nystagmus
EA5	CACNB4	Calcium voltage-gated channel $\beta 4$ subunit (Cav2.1)	Dysarthria, vertigo, nystagmus, and seizure
EA6	SLC1A3	Excitatory amino acid transporter 1	Weakness, seizure, vertigo, nystagmus, and dysarthria
EA7	Unknown	Unknown	Vertigo, weakness, and dysarthria
EA8	UBR4	E3 ubiquitin-protein ligase	Vertigo, weakness, myokymia, and slurred speech

are imbalance, incoordination, and slurred speech, triggered by physical and emotional stress or abrupt movements. Usually, episodes of attacks last seconds to minutes.

**EA type 2 (EA2)** is associated with nonsense mutations in the calcium channel gene, CACNA1A. The onset is typically early in life and the episodes of recurrent ataxia, such as slurred speech, can usually last for several hours, and patients present various forms of interictal nystagmus such as gaze-evoked nystagmus, rebound nystagmus, or primary position downbeat nystagmus.<sup>103–105</sup> Vertigo and general weakness are commonly present and patients gradually develop cerebellar symptoms.

### Other EA subtypes

Other EA subtypes have been reported in small group of families. EA3 was first described in a single large Canadian family.<sup>106</sup> EA4, also termed as periodic vestibulocerebellar ataxia, was originally characterized in two kindreds, suggesting a single common founder.<sup>107</sup> EA5 is caused by a mutation in the gene encoding for the calcium channel CACNB4, identified in a French Canadian family.<sup>108</sup> EA6 is attributed to a mutation in SLC1A3, identified in two separate individuals.<sup>109,110</sup> See Table 2 for a complete list of mutations and symptoms related to EAs.

### Treatment perspectives

Like with most neurodegenerative diseases, no cure or prevention of the cerebellum-linked ataxias exists. Attempts to develop a symptomatic treatment for ataxia have not yet been very successful. Currently, emphasis of treatment for cerebellar disorders mainly involves improving the quality of life of patients. Lack of effective pharmacological options that successfully cure the underlying cause of cerebellar ataxia has led to focus on identifying symptoms associated with or caused by ataxia and treating those symptoms. This largely involves rehabilitation methods, which include speech and swallowing therapy, physiotherapy aimed at improving motor coordination, and occupational therapy. Two large cohort studies have demonstrated the beneficial effects of motor rehabilitation on individuals with

degenerative cerebellar diseases.<sup>111,112</sup> A 12-h per week regime involving physiotherapy with occupational therapy in 42 patients suffering from degenerative cerebellar ataxias led to remarkable improvements in ataxia severity, fall frequency, and activities of daily living measured by the Functional Independence Measure.<sup>113</sup> Interestingly, patients exhibiting predominant trunk ataxia presented much more noticeable improvements as compared to patients having limb ataxia. Moreover, patients with mild ataxia severity had a longer sustained improvement in ataxic symptoms and gait speed.<sup>112</sup>

### Genetic targeting of PolyQ expansion in SCAs and FRDA

For PolyQ expansion-related dominant SCAs, therapeutic efforts largely involve inhibiting the expression of PolyQ proteins via antisense oligonucleotides (ASOs) or artificial microRNAs (miRNAs) or viral-mediated delivery of short hairpin RNAs to interfere with the translation of PolyQ. Most positive readouts for this type of approaches being successful come from preclinical studies of ASOs or miRNA-centered therapeutic interventions for SCA1, SCA3,<sup>114</sup> and SCA6.<sup>115</sup> Remarkably, SCA2 ASOs were not only able to reduce pathological hallmarks in SCA2 mice model,<sup>116</sup> but they were also able to reduce the disease burden in the mouse model of TDP-43-associated amyotrophic lateral sclerosis.<sup>117</sup> In terms of prospective delivery of ASOs, the experience and clinical trial success of ASO-based therapy in children for another degenerative disease, spinal muscular atrophy via lumbar puncture,<sup>118,119</sup> and phase I clinical trial for ASOs in Superoxide dismutase 1 (SOD1)-mediated ALS<sup>120</sup> provide proof that CNS delivery of PolyQ-targeting ASOs is a feasible approach in the near future. In preclinical rodent model of FRDA, hypertrophic cardiomyopathy was reversed via intravenous injection of adeno-associated virus rh10 vector expressing human FXN, and administration of the frataxin-expressing viral vector, after the onset of heart failure, was able to normalize the cardiomyopathy of these mice at the functional, cellular, and molecular levels.<sup>121</sup>



## Pharmacological compounds for the treatment of cerebellar disorders

Aminopyridines (APs) are inhibitors of the potassium channels, mainly blocking Kv1 family of voltage-activated potassium channels. Antagonizing the activity of these channels leads to increased excitability of neurons, especially of cerebellar Purkinje cells as well as of other cerebellar neurons.<sup>122</sup> In preclinical mouse model of EEA2, 4-aminopyridine (4-AP) and closely related compound 3,4-diaminopyridine improve the precision of pacemaker firing of Purkinje cells,<sup>123</sup> reducing the frequency of ataxia attacks.<sup>124</sup> Similarly, AP normalizes and improves the firing rate of Purkinje cells and motor behavior in ataxin-1 mutant mice.<sup>125</sup> Importantly, in patients with A-T, 10 mg of 4-AP treatment restored the vestibulo-cerebellum-mediated inhibition on to the deep cerebellar nuclei, thereby reducing the time constant of the angular vestibulo-ocular reflex and improving the quality of life of patients.<sup>126</sup>

Besides cerebellar ataxias and gait disorders, 4-AP is currently being recommended for the symptomatic control of varied neurological dysfunctions such as in multiple sclerosis, downbeat and upbeat nystagmus.<sup>127</sup> Furthermore, some EA2 and SCA6 patients show a beneficial response to an anti-epileptic drug, acetazolamide.<sup>128</sup> Randomized controlled trial of riluzole on a mixed group of patients presenting varied forms of dominant and recessive ataxia exhibited an improvement in the severity of symptoms after 2 or 12 months of treatment.<sup>129,130</sup> In yet another randomized controlled trial of SCA3 patients, treatment with the acetylcholine receptor agonist varenicline showed beneficial effects on gait-related symptoms.<sup>131</sup> Histone deacetylase inhibitor treatment regime of 30–240 mg/day was well tolerated in FRDA patients and increased *Frataxin* mRNA in peripheral blood mononuclear cells.<sup>132</sup>

## Conclusion

The availability of newer drugs and treatment regime largely depends on the speed at which research and new rapid diagnostic technologies are developed. Current need is to expand translational and back-translational research in preclinical animal models, in parallel enhance the development of novel animal models for rare cerebellar ataxias, and to establish new imaging techniques, which would shed continuous light on the pathology of cerebellar ataxias. Since cerebellar ataxias by nature are quite diverse, implicating genetic, clinical, and pathophysiological heterogeneity, the task of identifying novel therapies targeting wide-ranging forms of ataxia remains challenging. Moreover, the uncommonness and the geographic restriction of some forms of ataxia make large randomized controlled trials difficult. Multicenter, multinational, and even intercontinental efforts are needed to conclusively provide novel therapies and cure from the underlying cause of ataxia.


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